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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
AKHAVAN, RAMIN	
ART UNIT	**PAPER NUMBER**
1636	

DATE MAILED: 03/28/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

3/21/05

Office Action Summary	Application No.	Applicant(s)	
	09/868,411	KORNOWSKI ET AL.	
	Examiner	Art Unit	
	Ramin (Ray) Akhavan	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *20 December 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-5,7-9,12,14-18,31,87,90,94-96 and 103* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-5,14-16,18,87,94-96 and 103* is/are rejected.

7)☐ Claim(s) *7-9,12,17 and 90* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Acknowledgment is made of an amendment/response, filed 12/20/2004, canceling claims 6, 10-11, 13, 19-30, 32-86, 88-89, 91-93 and 97-102, and amending claims 7, 8, 17, 31, 90 and 103. Claims 1-5, 7-9, 12, 14-18, 31, 87, 90, 94-96 and 103 are currently pending and under consideration in this action.

All objections/rejections not repeated herein are hereby withdrawn. All rejections set forth will express whether the rejection is new or previously made. Where applicable, a response to Applicant's arguments will be included in the body of objections/rejections maintained. As new grounds of rejection are set forth, this action is non-final.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter, which the applicant regards as his invention.

1. **Claims 31 and 95 rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.**

This is a new ground of rejection. Claim 31 recites the term "prior to (b)" which confers ambiguity. Claim 31 is dependent from claim 17, intervening claims 14-16 and ultimately base claim 1, but none of the intervening claims recite a step denoted by the reference "(b)". Therefore as written, the claim is vague and indefinite.

Claim 95 recites the phrase, "composition of claim, further". As written the claim is vague because the proper claim dependency is omitted (i.e., claim 87 is the only claim directed to a composition).

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

2. Claim 103 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement.

This rejection was made previously and is repeated herein in salient part with respect to claim 103. A response to Applicant's arguments is set forth immediately following the body of this rejection. The claim contains subject matter, which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention. More particularly, the subject matter is drawn to direct administration of culture to heart or limb tissue in a method of enhancing angiogenesis in said tissue. The test for enablement is whether one skilled in the art could make and use the claimed invention from the disclosure in the specification coupled with information known in the art without undue experimentation. *United States v Telectronics Inc.*, 8 USPQ2d 1217 (Fed. Cir. 1988). Whether undue experimentation is required is not based upon a single factor but instead is a conclusion reached by weighing many factors which are outlined in *Ex parte Forman*, 230 USPQ 546 (Bd. Pat. App. & Inter. 1986) and *In re Wands*, 8 USPQ2d 1400 (Fed. Cir. 1988). The factors include the following:

Scope/Breadth of the claims. The claims are broad in the sense that they are directed to administration of any cultured medium containing any factor(s), wherein bone marrow aspirate has been grown from any source in said medium, and where the medium is directly administered to the heart in a subject to promote collateral blood vessel formation.

Nature of the invention. The invention encompasses promoting collateral blood vessel formation in the heart by administration of culture medium into a subject's heart.

State of the Art and Predictability. Currently it is not routine to administer cultured conditioned medium to ischemic tissue in patients. With respect to administration of ABM conditioned media (CM) to enhance angiogenesis, first, there would be unpredictability based on the ABM population or subpopulation being cultured as to whether produce in sufficient concentrations the necessary angiogenic factors necessary to promote angiogenesis in a given target tissue. Depending on the source of the bone marrow aspirate and the patient in whom the culture medium is administered, the results can be quite unpredictable (e.g., immune toxicity).

Furthermore, in regard to direct administration of media into a target site, there would be unpredictability based on the volume or frequency of injections with respect the likelihood of macro-aggregate formation (e.g., depending on what constituents comprise the culture medium) in response to the factors contained in the culture medium as well as blood clot formation. Therefore, administrating culture media directly into a subject to enhance angiogenesis is an unpredictable undertaking.

Amount of guidance provided. The only substantial guidance is limited to conditioned medium examined *in vitro* to show cell proliferation (Spec. p. 11, Example 1) or vascular tube formation (Spec. p. 16, Example 3).

As such no substantial guidance is provided with respect to in *vivo* unpredictability, such as with respect clot formation, immune toxicity or adverse effects that can result depending on what the source organism is for the bone marrow aspirate grown in the culture or what components are present in the culture medium. In sum, there is no significant guidance as to *in vivo* administration of conditioned medium to heart or limb tissue.

Number of working examples. As noted above, *in vitro* are provided to examine cell proliferation of pig aortic endothelial cells (Example 1). Furthermore, using said endothelial cells and vascular smooth muscle cells in a co-culture technique culture media effectuated endothelial cell tube formation.

Amount of Experimentation Required. The level of skill in the art required to practice the claimed invention is high. Given the unsolved hurdles to successful practicing of the invention, the level of unpredictability in the art and lack of relevant working examples, it must be considered that the skilled artisan would be required to conduct trial and error experimentation of an undue nature in order to attempt to practice the claimed invention.

Response to Arguments

Applicant's arguments are primarily directed to ABM transplantation thus are moot as the corresponding rejections have been withdrawn. With respect to claim 103, Applicant asserts that *in vivo* data is not necessary where the *in vitro* data is sufficient and animal model methods are provided. (Remarks, p. 11). Further, Applicant asserts that presence of one working example should not be the sole reason for making a scope of enablement rejection.

First, given the breadth of claim 103 (any bone marrow aspirate, any medium comprising any factors and administered to the heart of any patient), there would be unpredictability of results with respect to adverse outcomes related to immunotoxicity, resulting in unpredictability in practicing the claimed method. The *in vitro* examples provided do not address the immune toxicity to any substantial degree. Second, there are no animal models presented where conditioned culture medium alone is administered to the animal's heart. Furthermore, there are no animal models disclosed where the culture medium is undefined or where the source of the bone marrow aspirate can be from any organism.

With respect to the lack of animal models as the sole basis for a rejection, Applicant is correct that the totality of the circumstances surrounding all the Wand's factors must be considered in setting forth an enablement rejection. The enablement rejection herein and as set forth previously always provided a full consideration of all the Wand's factors. In sum, the arguments are not found persuasive in regard to claim 103, because the claim is broad, there is unpredictability in practicing the claimed method commensurate with the claim's scope, the guidance and examples provided are limited to *in vitro* cell proliferation assays, thus the artisan would undertake undue trial and error experimentation to practice the claimed method.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

The changes made to 35 U.S.C. 102(e) by the American Inventors Protection Act of 1999 (AIPA) and the Intellectual Property and High Technology Technical Amendments Act of 2002 do not apply when the reference is a U.S. patent resulting directly or indirectly from an international application filed before November 29, 2000. Therefore, the prior art date of the reference is determined under 35 U.S.C. 102(e) prior to the amendment by the AIPA (pre-AIPA 35 U.S.C. 102(e)).

3. Claims 87, 94 and 95 are rejected under 35 U.S.C. 102(b) as being anticipated by Nakahata (US Pat. 5,610,056; see whole document; hereinafter the '056 patent).

This rejection was made previously and is repeated herein. A response to Applicant's argument is set forth immediately following the body of this rejection. The claims are drawn to a composition comprising any cultured autologous bone marrow aspirate that has been stimulated in culture by exposure to a cytokine. The term "stimulated" is interpreted as broadly as reasonable, to include growth, migration, proliferation and differentiation. In addition, the term "conditioned medium" is interpreted as broadly reasonable to mean a medium in which ABM cells are grown. Further, the limitation "bone marrow aspirate" is not particularly limiting, thus is interpreted as broadly as reasonable to mean any population ob bone marrow cells.

The '056 patent teaches a composition comprising of medium that includes bone marrow derived stem cells, which are treated with the cytokine – IL-6. (e.g. col. 3, ll. 15-17).

The cells are grown in culture thus the composition necessarily comprises culture medium as well, which medium is conditioned by dint of the cells growing in the medium.

Response to Arguments

Applicant's arguments have been fully considered but they are not persuasive. Applicant asserts that the reference does not teach ABMs that have been stimulated by angiogenic growth factors or that ABM in conditioned medium promotes/stimulates angiogenesis or blood vessel formation. (Remarks, p. 12, middle). In sharp contradiction, Applicant next concedes that the reference teaches human stem cells that are induced to proliferate via interleukin-6 (IL-6) treatment, but Applicant goes on to assert that the reference is not enabling for compositions that promote or stimulate angiogenesis. (Id.)

Applicant's arguments present contradictions as to what the '056 patent teaches or does not teach, but nonetheless it is beneficial to review what is actually claimed. Base claim 86 broadly claims in salient part, "A composition comprising cultured autologous bone marrow aspirate that has been simulated ex vivo by exposure to hypoxia or *an angiogenesis stimulating cytokine*." (Emphasis added). Therefore, any composition comprising ABMs that have been treated with a stimulating cytokine would necessarily read on the claim. The claim does not recite any limitations having to do with the composition promoting or stimulating angiogenesis, contrary to what Applicant asserts. Furthermore, dependent claims 94 and 95 merely repeat that the medium is one in which the ABMs have been grown and that the composition comprises a protein that promotes cell proliferation, migration or blood vessel formation.

An intrinsic property of IL-6 is that it stimulates bone marrow cells and promotes blood vessel formation. (e.g., Aoki et al. Blood. June 1999; 93:4034-43; Absract; p. 4034, col. 1, last ¶ bridging to col. 2; teaching that IL-6 stimulates progenitor cells and accompanies neovascularization; this reference is merely provided to illustrate the intrinsic property of IL-6). However, for the purposes of the rejected claims, that IL-6 is a stimulating cytokine, without more, is sufficient to meet the instant claims.

Furthermore, the composition taught by the '056 patent is enabled for the stated purpose of promote production of erythroid cell proliferation using bone marrow cells. As written the claims read on the said composition, thus that Applicant intends a different use for the same composition does not obviate the basis for the rejection. Applicant's argument is based on a particular use for a composition the reads on the prior art composition. As stated above, the claims are directed to ABMs that are stimulated by any cytokine, thus the claims are anticipated.

4. **Claims 87, 94 and 95 are rejected under 35 U.S.C. 102(e) as being anticipated by Bauer et al. (US Pat. 5,997,860; see whole document; hereinafter the '860 patent).**

This rejection was made previously and is repeated herein. A response to Applicant's argument is set forth immediately following the body of this rejection. The '860 patent teaches a culture comprising autologous bone marrow where cells are exposed to the cytokines so as to stimulate the cells. (e.g. Abstract). More particularly, a list of various cytokines is provided, which includes interleukins 1-13, including IL-6. (e.g. col. 6, ll. 40-51). Furthermore, the cells are derived from bone marrow. (e.g. col. 8, ll. 28-30).

Since the cells are grown in culture medium, then the composition taught necessarily comprises culture medium. Therefore, the '860 patent anticipates the rejected claims.

Response to Arguments

Applicant's arguments have been fully considered but they are not persuasive. Applicant's first argument is that the '860 patent does not teach ABM composition in conditioned medium that promotes and stimulates angiogenesis or blood vessel formation and that the teachings of the '860 are not enabled.

Applicant's arguments are similar to the discussion above. (Supra, Rejection No. 3). In summary, the compositions as claimed read on the prior art composition. As stated above, IL-3 is a stimulating cytokine and where the '860 patent teaches a composition comprising ABMs and a stimulating cytokine, the '860 patent anticipates the rejected claims.

5. **Claims 1-4, 14-16, 18, 87, 94-96 and 103 are rejected under 35 U.S.C. 102(e) as being anticipated by Mickle et al. (US 2005/0031600 A1; see whole document; hereinafter Mickle).**

This ground of rejection is new. The claims are interpreted consonant with the interpretations stated above. In addition, it would be beneficial to address the interpretation for the limitation "aspirate". The term "aspirate" is not particularly delimited in the specification or in the claim. In addition, the claims utilize open language (i.e., "comprising"). Therefore, the limitation "aspirate" is interpreted as broadly as reasonable to mean any bone marrow aspirate, from which any bone marrow cell population is derived.

Mickle teaches transplantation of autologous bone marrow (ABM) cells into the heart tissue of an animal, whereby the transplantation results in angiogenesis, i.e., enhanced collateral blood vessel formation. (e.g., Abstract; ¶¶ 0009, 0043, 0047-0049, 0104, 0119: claim 1; ¶¶ 0111-113: claims 2-3). The autologous bone marrow cells are obtained from bone marrow aspirate. (e.g., p. 3, ¶ 0048). The ABMs are injected into the ischemic tissue using a syringe directly into the ischemic scar tissue, thus comprises endocardial injection. (e.g., p. 7, ¶ 0113; claims 4 and 18).

Alternatively the cells are administered in combination with a pharmacological drug, i.e., 5-azacytidine. (e.g., p. 1, ¶¶ 0010, 0015: claims 2-3 and 14-16). The ABMs are cultured *ex vivo* and subjected to the 5-azacytidine. (e.g., p. 1, ¶ 0015: claim 87). Treating ABMs with 5-azacytidine and transplanting such cells into the heart is known to improve function, where such improvement is measured among other assays, through angiogenesis. (e.g., Tomita et al. 1999; Circulation;100(suppl II): II241-56; p. 247, col. 2, ¶ 1; p. 251, col. 2, ¶ bridging to p. 252; this reference is of record and is merely presented to show the intrinsic property of the drug 5-azacytidine in promoting cardiac function through angiogenesis).

Culture medium alone is also administered to the ischemic heart tissue. (e.g., p. 7, ¶ 0113: claim 103). The cells are grown in culture and can contain 5-azacytidine, thus read on a composition comprising ABMs containing a conditioned medium in which said cells are grown and that further comprises a pharmacological agent (claims 87, 94-95). Furthermore, the marrow aspirate is transferred into a tube containing heparin. (e.g., p. 3, ¶ 0048; claim 96). Therefore, as the foregoing discussion sets forth, Mickle anticipates the rejected claims.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

6. **Claims 1-5, 14-16, 18, 87, 94-96 and 103 rejected under 35 U.S.C. 103(a) as being unpatentable over Mickle et al. (US 2005/0031600 A1) further in view of Mack et al. (J. Thorac. Cardiovas. Surg. 1998; 115: 168-77).**

This is a new ground of rejection. The claims are interpreted consonant with the interpretations discussed above. In addition, claim 5 is directed to trans-endocardial catheter injection of ABMs.

Mack et al. do not specifically teach a catheter approach, but teaches direct injection endocardially. (Supra, Rejection NO. 5).

Mack et al. teach catheter delivery of adenoviral vectors for delivery of vector-encoded VEGF to promote angiogenesis in ischemic heart tissue. (e.g., p. 169, col. 2, middle). Mack et al. teach that it would be beneficial to adopt direct delivery as taught, so as to preclude the possibility the promiscuous angiogenesis (e.g., p. 169, col. 1, middle). Therefore, where an angiogenic factor(s) is being administered to a subject's heart, Mack et al. teach that to obviate non-targeted angiogenesis direct delivery is preferred.

Mickle et al. teach that an agent (i.e., ABMs) is being delivered to enhance cardiac function, such as through angiogenesis, similar to Mack et al. delivering an agent (VEGF encoding vector) to enhance cardiac function. Therefore, it would have been obvious to one of ordinary skill in the art to utilize the catheter-based delivery system as yet another method of direct delivery, so as to expand the range of delivery options available in delivering an agent to promote angiogenesis and to obtain the benefit of diminished non-targeted angiogenesis. Given the level of skill in the art at the time of invention, there would have been a reasonable likelihood of success to implement the catheter-based direct delivery as taught by Mack et al. in place of the injection-based direct delivery as taught by Mickle et al.

Allowable Subject Matter

Claims 7-9, 12, 17 and 90 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

The closest art is that of Isner et al. (US Patent 6,676,937) which teaches a method of *in vivo* stimulation (e.g., with GM-CSF) to promote angiogenesis in ischemic tissue, but which isolates and cultures endothelial progenitor cells from the peripheral blood of a given subject.

Conclusion

Claims 1-5, 14-16, 18, 87, 94-96 and 103 are rejected. Claims 7-9, 12, 17 and 90.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ray Akhavan whose telephone number is 571-272-0766. The examiner can normally be reached between 8:30-5:00, Monday-Friday. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Remy Yucel, PhD, can be reached on 571-272-0781. The fax phone numbers for the organization where this application or proceeding is assigned are 571-273-8300 for regular communications and 703-872-9307 for After Final communications.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Respectfully submitted,

Ray Akhavan/AU 1636

GERRY LEFFERS
PRIMARY EXAMINER